items, the Examiner has not been able to confirm the presence of these materials in the file.

Applicant is now submitting copies of all materials originally submitted on October 12, 2001. These include: the sequence listing in computer readable and paper formats, Statement to Support Filing and Submission In Accordance with 37 C.F.R. § 1.821-1.825, and a Preliminary Amendment inserting sequence identifiers (SEQ ID NOS) 1 and 12-114 into the specification and claims.

In the current response, Applicants have further amended the specification and claims to insert sequence identifiers (SEQ ID NOS) for sequences 2-11.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the paragraph beginning on page 4, line 21 as follows:

Figure 5 illustrates the sequence-specific interactions selected at position 2 of the α-helix, binding to position 1 of the quadruplet.[for which sequence identifiers are shown.] Sequence identifiers 79, 78 and 59 are depicted in figure 5A, while figure 5B depicts SEQ ID NOS: 20, 21, 62, 63, 75, 78, 80, 50, 72, 110, 89, 81, 82, 53, 43, 46, 70 and 71 respectively.

Please amend the paragraph beginning on page 15, line 1 as follows:

In general, a preferred zinc finger framework has the structure:

(A) X_{0-2} C X_{1-5} C X_{9-14} H X_{3-6} H/C (SEQ ID NO:4)

Please amend the paragraph beginning on page 15, line 9 as follows:

In a preferred aspect of the present invention, zinc finger nucleic acid binding motifs may be represented as motifs having the following primary structure:

(B) X^a C X_{2-4} C X_{2-3} F X^c X X X X L X X H X X X^b H – linker (SEQ ID NO:5)

-1 1 2 3 4 5 6 7 8 9

wherein X (including X^a, X^b and X^c) is any amino acid. X_{2-4} and X_{2-3} refer to the presence of 2 or 4, or 2 or 3, amino acids, respectively. The Cys and His residues, which together co-ordinate the zinc metal atom, are marked in bold text and are usually invariant, as is the Leu residue at position +4 in the α-helix.

Please amend the paragraph on page 16, line 18 as follows:

Preferably, the linker is T-G-E-K (SEQ ID NO:6) or T-G-E-K-P (SEQ ID NO:7).

Please amend the paragraph beginning on page 18, line 4, as follows:

Consensus zinc finger structures may be prepared by comparing the sequences of known zinc fingers, irrespective of whether their binding domain is known. Preferably, the consensus structure is selected from the group consisting of the consensus structure P Y K C P E C G K S F S Q K S D L V K H Q R T H T G (SEQ ID NO:8), and the consensus structure
P Y K C S E C G K A F S Q K S N L T R H Q R I H T G E K P (SEQ ID NO:9).

Please amend the paragraph beginning on page 18, line 10, as follows:
The consensuses are derived from the consensus provided by Krizek *et al.*, (1991) J. Am. Chem. Soc. 113:4518-4523 and from Jacobs, (1993) PhD thesis, University of Cambridge, UK. In both cases, the linker sequences described above for joining two zinc finger motifs together, namely TGEK (SEQ ID NO:6) or TGEKP (SEQ ID NO:7) can be formed on the ends of the consensus. Thus, a P may be removed where necessary, or, in the case of the consensus terminating T G, E K (P) can be added.

Please amend the paragraph beginning on page 19, line 15, as follows:
A "leader" peptide may be added to the N-terminal finger. Preferably, the leader peptide is MAEEKP (SEQ ID NO:10).

Please amend the paragraph beginning on page 33, line 6, as follows:
Library selections are carried out using DNA binding sites that resembled the Zif268 operator, but which contained systematic combinations of bases in the DNA doublet which forms the base-step between the DNA subsites of F2 and F3. DNA binding sites are of the generic form 5'-GNX-XCG-GCG-3' (SEQ ID NO:1), where X-X denotes a given combination of the bases at the interface between the DNA subsites, and N denotes that the four bases are equally represented at DNA position 3. Thus the interaction between F3[+3] and nucleotide position 3N is allowed complete freedom in this experiment. This feature of the library allows selection of a large family (or database) of related zinc fingers that bind a given combination of bases at nucleotide positions 4X and

5X, but which are non-identical owing to different interaction with the middle base in the nominal triplet subsite of F3.

Please amend the paragraph beginning on page 33, line 18, as follows:

The first library to be constructed, LIB-A, contains [randomisations] randomizations at F2 residue position 6 and F3 residue positions –1, 1, 2 and 3 (see Figure 2), and is sorted using the DNA sequence 5'GNX-XCG-GCG-3' (SEQ ID NO:1), where X-X denotes a known combination of the two bases at DNA positions 4X and 5X, and N denotes an equal probability of any of the four bases at DNA position 3. The second library, LIB-B, contains [randomisations] randomizations at F2 residue position 6 and F3 residue positions –1 and 2, and is sorted using the DNA sequence 5'-GCX-XCG-GCG3' (SEQ ID NO:2), where X-X denotes a known combination of the two bases at DNA positions 4X and 5X.

Please amend the paragraph beginning on page 39, line 29, as follows:

Selections are performed using the DNA sequence GCG-GMN-OPQ (SEQ ID NO:3) for LIB 1/2 and the DNA sequence IJK-LMG-GCG (SEQ ID NO:11) for LIB 2/3, where the underlined bases are bound by the WT Zif268 residues and each of the other letters stands for any given nucleotide. The conserved nucleotides of the Zif268 binding site serve to fix the register of the interaction by binding to the conserved portion of the Zif268 DNA-binding domain. The binary phage display libraries can be mixed so that selections using these two generic sites are performed in a single tube, or the selections can be performed separately. After a number of rounds of selection the two libraries are recombined to produce a chimeric DNA-binding domain that [recognises] recognizes the sequence IJK-LMN-OPQ.

In the claims:

Please amend claim 10 as follows:

10. (Amended) A library according to any preceding claim, wherein each zinc finger has the general primary structure

(A) X^a C X_{2-4} C X_{2-3} F X^c X X X X L X X H X X X^b H – linker (SEQ ID NO:5)

-1 1 2 3 4 5 6 7 8 9

Please amend claim 15 as follows:

15. (Amended) A library according to any one of claims 10 to 14 wherein the linker is T-G-E-K (SEQ ID NO:6) or T-G-E-K-P(SEQ ID NO:7).

Please amend claim 20 as follows:

20. (Amended) A method according to claim 19, wherein the model zinc finger is a consensus zinc finger whose structure is selected from the group consisting of the consensus structure

P Y K C P E C G K S F S Q K S D L V K H Q R T H T G (SEQ ID NO:8), and the consensus structure

P Y K C S E C G K A F S Q K S N L T R H Q R I H T G E K P (SEQ ID NO:9).